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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,436	02/19/2003	Peter Carmeliet	50304/116001	1656

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EXAMINER	
MONTANARI, DAVID A	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,436	CARMELIET ET AL.	
	Examiner	Art Unit	
	David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-44* is/are pending in the application.

4a) Of the above claim(s) *39-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group VI claims 32-38 in the reply filed on 3/27/2006 is acknowledged. The traversal is on the ground(s) that claim 39 relates to a single inventive concept that includes the use of Gas6 inhibitors in the treatment of endothelial activation and dysfunction. This is not found persuasive because applicants have cancelled the original claims of Group VI in the previous restriction requirement and have present new claims 32-44, which applicants have withdrawn claims 39-44. As discussed in the telephone interview conducted on March 9, 2006, applicants have cancelled the originally restricted claims 1-31, and provided new claims drawn to more than one group, thus applicant has provided the current instant claims. The restriction requirement did not contain claims drawn to the subject matter in claims 39-44, thus the issue of traverse is moot. Applicant has voluntarily withdrawn claims 39-44.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 39-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/19/2005.

3. Claims 32-38 are examined in the instant application.

Specification

The instant specification is missing Cross-References to Related Applications: See 37 CFR 1.78 and MPEP § 201.11. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 32-38 are drawn to a method of treatment or prevention of endothelial dysfunction or sepsis comprising administering a soluble Gas6 receptor to a patient. Wherein said endothelial dysfunction is caused by endotoxin or surgery.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not

disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of the claims encompasses treating or preventing any endothelial dysfunction or sepsis using a soluble Gas6 receptor. This embodiment reads on protein therapy.

Whereas the nature of the invention is a method of treating or preventing endothelial dysfunction or sepsis by delivering a soluble Gas6 receptor to act as an inhibitor of Gas6 function, the art of protein delivery for the treatment of disease is unpredictable. At the time the invention was made, successful implementation of protein therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by several reviews. Brown (2005, Expert Opinion Drug Delivery, Vol. 2(1), pgs. 29-42) discusses the many challenges that surround protein delivery and therapy. Brown teaches that proteins are commonly delivered by three routes: oral, nasal, and pulmonary (pgs. 31-33). Specifically, each has it's own challenges, with oral delivery requiring the avoidance of proteolytic enzymes and the absorbance of relatively large molecules (proteins) through a membrane that is designed to actively uptake only single amino acids, dipeptides or tripeptides (pg. 31 col. 2 parag. 2). Nasal delivery is hampered by a low bioavailatibility of the medic being delivered due to the limited area that can absorb the therapeutic. Brown teaches that low molecular weight moieties will be the most successfully for delivery via the nasal pathway, with doses from 0.2 to 400 ug (pg. 33 col. 1 parag. 3). Regarding pulmonary delivery of proteins, the main challenge is obtaining effective systemic delivery via the lungs to the alveoli or deep lung (pg. 33 col. 1 last 2 lines bridge col. 2 line 1). Brown teaches that insulin has been an exemplary protein for delivery via the pulmonary route, but that

"formulating proteins such that they maintain their stability and that they are delivered within their efficacious and safe target doses remains a challenge" (pg. 39 col. 2 parag. 3).

Regarding the issue of delivery a protein to the body for treatment significant issues arise especially when the protein is produced recombinantly for treatment. The breadth of the claims encompasses the recombinant manufacture of soluble Gas6 since the instant specification is silent regarding the production, delivery, or treatment using soluble Gas6 receptor. Hayes et al. discuss this in detail (1997, Clinical Immunology and Immunopathology, Vol. 83, pgs. 1-4). Hayes teaches specific endogenous mechanisms that exist to interfere with the delivery of proteins, mainly neutralizing antibodies (pg. 3 col. 2 parag. 6-7 bridge col. 1). Hayes continues that toxicology studies are important to determine the risk of systemic exposure to a recombinant protein, and that "artificial administration of a recombinant protein in a disease state cannot mimic the normal endogenous milieu at the site of disease or in normal tissue, where no effect is usually desired" (pg. 1 col. 2 last sentence bridge pg. 2 col. 1 lines 1-2). Hayes continues that a protein is often injected at a high dose causing exaggerated pharmacodynamic effects which can be adverse, and that many recombinant proteins are pluripotent the desired effect has limited specificity (pg. 2 col. 1 parag. 1-2).

Addressing the issue of blocking Gas6 function by administration of soluble Gas6 receptor acting as an inhibitor, the art teaches that Gas6 has power anti-apoptotic properties in vascular smooth muscle cells. Thus inhibition of a potent anti-apoptotic could lead to further deleterious effects. Melaragno et al. discuss the role of Gas6 in apoptosis in detail (2004, J. Mol. Cellular Cardiology, Vol. 37, pgs. 881-887). Melaragno et al. teach that high concentrations of Gas6 completely prevented cell death in serum deprived induced cell death of NIH3T3

fibroblasts, and that Gas6 was unable to rescue Axl (downstream Gas6 receptor) knockout mouse fibroblasts from apoptosis (pg. 882 col. 1 parag. 1). Melaragno et al. continue that using lower concentrations of Gas6 rescued human umbilical vein endothelial cells from serum deprivation- and tumor necrosis factor alpha-induced apoptosis (pg. 882 col. 1 parag. 1). Melaragno et al. continue to teach that Gas6 binding to the tyrosine kinase receptor Axl inhibits apoptosis in cultured VSMC via pathways dependent upon Axl phosphorylation and Akt activation (pg. 885 col. 2 parag. 1 lines 1-4). The above mentions teachings taken together teach that delivery of proteins is complex and requires significant experimentation, and potentially is non-beneficial when examined in view of recent research concerning Gas6 as an anti-apoptotic mediator.

The working examples provided by the instant specification teach that Gas6 deficient transgenic mice were generated via homologous recombination (pg. 7 lines 5-10). The specification continues that Gas6 was studied in said transgenic mice for roles in arterial stenosis, stroke, angiogenesis, and response to endotoxin (Examples 2-4). The specification continues to teach that various cytokines, factors, and interleukins were studied to observe the impact of Gas6 deficiency in a transgenic mouse model (Tables 1-7). However the specification fails to teach a method of treatment or prevention of endothelial dysfunction in a patient comprising administering a soluble Gas6 receptor. The instant specification provides no guidance to the skilled artisan that would enable the treatment or prevention of endothelial dysfunction caused by surgery or sepsis. The instant specification teaches only that Gas6 has a role in endothelial cell survival in response to various stimuli in a transgenic mouse model. Further there is no teaching in the specification how the skilled artisan would be guided using a transgenic mouse comprising a complete disruption of Gas6, as taught in the specification, to

guide the skilled artisan to treat or prevent endothelial dysfunction. The transgenic mice taught in the specification comprise a complete abolishment of Gas6, whereas the Gas6 signal transduction pathway would be established in a patient, which would have it's subsequent upstream and downstream signaling pathways. The instant specification fails to teach or link how the transgenic mouse taught in the examples would guide the skilled artisan to appropriately treat or prevent endothelial dysfunction by administering a Gas6 inhibitor. Further the phenotype of the transgenic mouse taught in the specification revolves around the complete abolishment of Gas6 production, however as stated above a treated patient will have Gas6, and would require significant research by the skilled artisan to adequately dose the required amount of abolishment to achieve the phenotypic results obtained in the transgenic mouse taught. As discussed above, significant issues regarding the unpredictability of the claimed method exist that would require further research and study to implement the claimed method. The instant specification does not further provide any additional teaching to the skilled artisan that would enable the claimed method over the teachings in the art discussed above. Thus the skilled artisan would require and undo amount of experimentation without a predictable degree of success to make and use the claimed method.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 32 recites the limitation "said patient" in reference to the previous line in claim 32. However there is no recitation of "patient" preceding "said patient". There is insufficient antecedent basis for this limitation in the claim.

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is 1-571-272-3108. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 1-571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

David A. Montanari, Ph.D.

DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER